REMARKS

The Amendments

The claims are amended to specify the steroid as being ciclesonide.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 1, 3-10, 15-23, 25-39 and 63-66 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement, is respectfully traversed.

The rejection is made based on the allegation that the specification does not enable one of ordinary skill in the art to make and use the solvates or hydrates (hydrate being a solvate where the solvent is water) of the compounds as claimed. The rejection is based on an analysis of the Wands factors and applicants address these factors below. However, applicants urge that there are other threshold issues to consider before the Wands factors.

Initially, applicants point out that the rejection appears to be largely based on an incorrect characterization of the claims. It is alleged in the Office Action that the claims include "thousands of steroids and tiotropium salts." But this is clearly incorrect because tiotropium is a specific compound. And by the above amendment, the second component (the steroid) is also one specific compound, i.e., ciclesonide. Thus, the claims are very narrow. For this reason alone, the reasoning of the rejection appears to be incorrect and the rejection should be withdrawn. However, the following further arguments are provided to address the rejection as a whole.

Although the Examiner is certainly aware of this, applicants want to reiterate that adequate enablement of a claim is not viewed merely by what is in applicants' specification. The knowledge of those of ordinary skill in the art must also be considered; see, e.g., see DeGeorge v. Bernier, 768 F.2d 1318, 226 USPQ 758 (Fed. Cir. 1985). See also, Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987), stating: "a patent need not teach, and preferably omits, what is well known in the art."

The position taken in the Office action is that formation of solvates or hydrates is not routine and is highly unpredictable. Applicants believe that this conclusion was arrived at because the wrong question is being considered. The conclusion in the Office action is based on the question of whether it is routine or predictable – without conducting any experimentation – to determine whether a specific solvent or water will form a solvate or hydrate with a specific compound and what the nature of such solvate or hydrate is. The correct question should be: Can one of ordinary skill in the art conduct routine experimentation to provide the solvates and hydrates of the claimed compounds which would be useful for carrying out the invention and can one of ordinary skill in the art routinely determine the nature of any such solvates or hydrates? Applicants submit that this later question is the proper one because the law is clear that adequate enablement can be provided from the knowledge available in the art and can be provided from one of ordinary skill in the art conducting routine experimentation (see cited cases above and below). Under this correct standard, there is adequate enablement for one of ordinary skill in the art to make and use solvates or hydrates of the claimed invention.

In the art of providing pharmaceutical compounds, one of ordinary skill in the art is well aware of the definition of the terms solvate and hydrate and the chemical structure of any theoretically possible solvate or hydrate for a given compound. Further, in this art it is

conventional to provide solvates or hydrates of pharmaceutical compounds. It only requires routine experimentation for one of ordinary skill in the art to determine what, if any, solvates or hydrates of a given compound can be provided. Providing solvates or hydrates of pharmaceutical compounds is common in the field and highly automated techniques allowing thousands of solvate formation tests at a time are available in the art. Thus, determining what solvates or hydrates for the two specific components of the instant claims could be practically obtained is routine in this field. Furthermore, applicants refer to the attached Decision from the Board of Patent Appeals and Interferences in Appeal No. 2000-0600 (page 9). The Decision shows that, in at least one case, the Board agreed with applicants that for a pharmaceutical compound "selection of appropriate solvents for forming solvates was routine to one of ordinary skill in the art" and "the metes and bounds of the term were reasonably determinable using only ordinary skill in the art." These facts support that providing solvates or hydrates of the compounds was routine in the art.

As a further basis for traversal of the rejection, applicants urge that, before even considering the Wands factors, a threshold burden lies with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims to support a rejection under 35 U.S.C. §112, first paragraph, for lack of enablement. See, e.g., MPEP §2164.04 citing In re Marzocchi et al., 169 USPQ 367 (CCPA 1971), which states:

> ".. a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein..",

and further,

> "..it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." (emphasis original).

In the instant case, the specification disclosure corresponds in scope with the claims since its general description of making and using the invention applies to the full scope of claimed compounds, which the disclosure makes clear (see, e.g., page 3, lines 24-28) includes the solvates and hydrates thereof. The Office action fails to provide any allegation that the truth or accuracy of the inventors' disclosure is doubted. Nor has any convincing explanation or evidence been provided to support why the Examiner doubts the truth or accuracy of the inventors' disclosure. In the absence of such an explanation or supporting evidence, the PTO's initial burden is not met and a lack of enablement rejection cannot be made. The Office action appears to be improperly shifting the burden upon applicants to provide experimental evidence of making and using solvates and hydrates of the compounds. But this burden is misplaced in the absence of the PTO meeting its initial burden. Applicants urge for this additional reason, that the rejection for lack of enablement should be withdrawn.

Taking consideration of all of the above points, applicants assess the Wands factors and the comments thereon in the Office action as follows.

The Breadth of the Claims – The breadth of the claims is quite narrow, as discussed above. The claims are directed to a composition comprising two components wherein each component is defined as a specific compound but including the enantiomers, solvates and hydrates thereof. The fact that solvates and hydrates are included does not make the scope of the claims broad. There is no basis to conclude that the claims embrace thousands of solvates (including hydrates) of the compounds. To the contrary, based on the knowledge available to one of ordinary skill in the art, one can only conclude that there would be limited number of

solvates/hydrates applicable for a pharmaceutical composition and one of ordinary skill in the art can routinely determine what they are.

The Nature of the Invention – The Office action alleges that the nature of the invention is the synthesis of solvates and hydrates. Applicants respectfully disagree. The principal nature of the compositions of the invention is that it combines the tiotropium compound, the ciclesonide compound and the particular exicipient. That solvates and hydrates of the two principal components are included is not a principle characterizing feature of the invention. The correct defined nature of the invention does not support any conclusion that the invention is not enabled.

The State of the Prior Art – The state of the prior art is discussed above, i.e., the fact that it is routine in the pharmaceutical arts to determine and provide solvates or hydrates of compounds. Applicants also take note of the fact that the claims in a large number of patent applications directed to compounds in the pharmaceutical field include the recitation of solvates and/or hydrates therein without specifically describing preparation of them in the specification. This further evidences the conventional nature in the art to make and use solvates and hydrates. The Vippagunta article cited in the Office action does not support that one of ordinary skill in the art could not make and use solvates or hydrates of a particular compound. Vippagunta may support the notion that one of ordinary skill in the art cannot accurately predict beforehand whether a particular compound will form a solvate or hydrate with a particular solvent or what the nature of the resulting solvate or hydrate would be. But, as discussed above, this is not the proper inquiry. The article supports that only routine experimentation by one of ordinary skill in the art is needed to identify, provide and characterize suitable solvates or hydrates of a given compound. For example, *Vippagunta* on page 15, top of first column, states:

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement:

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling … Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states:

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. … The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof throughout its disclosure; see, e.g., pages 15-18. *Vippagunta* thus demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to prepare solvates and hydrates and how such solvates/hydrates would be identified or characterized, e.g., by polarized light microscopy, etc. See the extensive list of techniques identified on column 2 of page 18. While some experimentation would be required, such would just be routine to those of ordinary skill in the art. Further, it would be routine in the art to determine whether or not solvates or hydrates are possible for any specific compound. While predictions absent any experimentation may be difficult in the art of forming solvates or hydrates, the formation of solvates (and particularly hydrates) is common with pharmaceutically active ingredients and methods of preparing and characterizing them are well-known and widely applied routinely. In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that determining and providing solvates and hydrates of the compounds, as recited in the claims, would be well within the ordinary

skill in the art with routine experimentation.

The Level of One of Ordinary Skill in the Art – The Office action's characterization of the level of ordinary skill in the art is based on what applicants believe is an improper characterization of the nature of the invention, as noted above. The proper level of skill should be assessed based on the level of those researching to find new pharmaceuticals. The ordinary level of skill in this art is high, which supports enablement. The level of skill in this art would generally be that of a Ph.D. organic chemist, who would be more than adequately trained to direct or conduct the routine experimentation needed to prepare those hydrates and solvates of the two specific components claimed which can practically be provided.

The Level of Unpredictability in the Art – The Office action makes the vague allegation that everything related to chemical reactions is unpredictable; citing case law from the early '70s. Applicants disagree with such a broad characterization and find no support for such a position in fact or in the current law. There is no support on the record to find that one of ordinary skill in the art could not make and use solvates or hydrates of a particular compound. It may be true that one of ordinary skill in the art cannot accurately predict – beforehand – whether a particular compound will form a solvate or hydrate with a particular solvent or what the nature of the resulting solvate or hydrate would be. But, as discussed above, this is not the proper inquiry. While some experimentation would be required, such would just be routine to those of ordinary skill in the art. Further, it would be routine in the art to determine whether or not solvates or hydrates are possible for any specific compound. While certain predictions may be difficult in the art of forming solvates or hydrates, the formation of solvates (and particularly hydrates) is common with pharmaceutically active ingredients and methods of preparing and characterizing them are well-known and widely applied routinely. In any event, that there is some unpredictability and that some

experimentation may be needed do not negate a finding of adequate enablement. The rejection is based in part (i.e., in part (a)) on the allegation that experimentation would be required to provide the solvates or hydrates of the compounds. The Office action appears not to take consideration of whether such experimentation is merely routine, in which case enablement is not supported. The standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).

The Amount of Direction Provided – The Office action further alleges that the specification provides no guidance on how to make the solvates and hydrates encompassed by the invention. However, it was routine for one of ordinary skill in the art to make solvates or hydrates. As stated above, "a patent need not teach, and preferably omits, what is well known in the art." Spectra-Physics.

The Existence of Working Examples – It is well established that no working examples are required to establish enablement; see, e.g., In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and, In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Particularly in cases like the present, where the allegedly un-exemplified subject matter is a routinely provided derivative of the compounds for which working examples are provided, the presence or absence of working examples would be of minimal relevance in determining enablement. Merely because applicants' specification provides no examples of forming solvates or hydrates of the compounds, is not proof that it is not possible for the compounds to form solvates or hydrates. Again, the proper question is whether one of ordinary skill in the art can routinely determine what solvates or hydrates of the claimed compounds, if any, can be made and used according to the invention. The claims are only directed to those solvates or hydrates of the claimed compounds which can be made. If there are not any such solvates or

hydrates, then obviously the claims do not cover them. For example, see, e.g., Atlas Powder Co. v E.I. DuPont De Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984), stating: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude .. possible inoperative substances.'" The fact that not every compound can be made as a hydrate or a solvate is not a basis for alleging undue experimentation. This was clearly the finding of In re Wands, where high-affinity monoclonal antibodies were found enabled even though not every experiment would be expected to produce one. The entire surrounding circumstances must be considered, including the nature and quantity of the experimentation needed to arrive at hydrates and solvates and the other Wands factors.

The Quantity of Experimentation Needed – The requirement for some experimentation – even a large amount – does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine experimentation to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., In re Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also Ex parte Jackson, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to

practice a desired embodiment of the invention claimed." The conventionality in the art of providing solvates or hydrates and the existence of automated crystallization systems which allow thousands of crystallization experiments to find solvates in a short time makes their provision routine, rather than undue, regardless of the amount of experimentation needed.

Considered as a whole, applicants urge that the Wands factors also support that the claims are reasonably enabled.

For the above reasons, it is urged that the specification taken in view of the knowledge of those in the art provides an adequate description of how to make and use the claimed invention. Thus, the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

The Provisional Obviousness-type Double Patenting Rejections

The provisional obviousness-type double patenting rejections over each of copending application nos: 10/392,558; 10/735,959; 11/006,940; 11/068,134; 11/109,094; 11/169,876; 11/267,354; and, 11/424,244; are respectfully traversed.

Applicants urge that the instantly claimed subject matter is patentably distinct from the subject matter claimed in the copending applications. The instant claims are directed to a very specific combination of a tiotropium compound, a ciclesonide steroid compound and a particular type of excipient. None of the claims in the copending applications are directed to such a specific combination of components. Some of the copending claims contain comprising language which leaves their interpretation open to other components, but the possibility for arriving at compositions meeting the claimed requirements from such claims is far to remote to be considered patentably indistinct. Only the '940 application contains claims which could be argued as being directed to the same type of invention and, even the

claims in this application are remote from the instant claims because they are so much more broad. In every other case, the copending claims require a component which is not required by the instant claims and/or the copending claims do not require a component which is required by the instant claims. None of the copending claims provide any suggest to the specific combination of a tiotropium compound, a ciclesonide compound and the particular excipient of the instant claims. The claims of the '134 application require a water/ethanol solvent and do not require the instantly claimed excipients. The claims of the '094 application require a different type of anticholinergic compound and only broadly refer to optional additional actives. The claims of the '876 application are directed to particular aerosol formulations for which the excipients used in the claimed invention would not be useful. The '354 application is abandoned, thus, no provisional rejection based thereon is warranted. The claims of the '244 application do not recite ciclesonide-containing compositions. The claims of the '959 application require no steroid component, whatsoever, let alone ciclesonide. The claims of the '558 application consist essentially of the listed components and require no steroid, whatsoever, let alone ciclesonide. In view of the distinction in the claimed subject matter, the provisional rejections should be withdrawn.

Applicants reserve the right to further traverse these provisional rejections on additional bases for showing that distinct subject matter is being claimed (or that the claims may change to make them distinct). However, applicants further submit that these provisional rejections should be withdrawn because all of these applications were filed after the effective US filing of the instant application. Based on its parent filing date, the instant application is the first filed of all of these applications (note, however, that the 11/006,940 application is a CIP application of an application which is the same as the parent of the instant application). In accordance with MPEP §804(I)(B)(1) "the examiner should withdraw

the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue." Since all the other rejections are believed to be overcome, the provisional obviousness-type double patenting rejections based on these later-filed applications should be withdrawn.

The Rejection under 35 U.S.C. §103

The rejection of claims 1, 3-10, 15-23, 25-39 and 63-66 under 35 U.S.C. §103, as being obvious over the combination of Nishimura (Allergology) and Banholzer (U.S. Patent No. 5,610,163), is respectfully traversed.

Nishimura discloses the use of a combination of oxitropium bromide with a certain inhaled corticosteroid, i.e., beclomethasone diproprionate, for use in treating chronic asthma. Nishimura suggests that the combination of the oxitropium bromide provided advantages over beclomethasone diproprionate alone.

Banholzer discloses a generic formula (I) encompassing a range of compounds which includes tiotropium salts. Claim 5 is directed particularly to tiotropium salts.

The basis for the rejection is that it would have been obvious to one of ordinary skill in the art to exchange the oxitropium bromide of Nishimura with the tiotropium compound disclosed in Banholzer. Applicants respectfully submit that such a combination would not meet or suggest the elements of the claims and, thus, not support a prima facie case of obviousness. Further, applicants urge that, even if the references establish a prima facie case of obviousness, evidence of unexpected advantages for applicants' particular combination overcomes any prima facie case of obviousness.

The instant claims recite a combination of the tiotropium compound and the particular steroid, ciclesonide. Neither of the references provide any suggestion to combine the particular steroid ciclesonide. Nishimura discloses only a beclomethasone salt and Banholzer provides no teachings regarding any steroid. The combined reference teachings thus fail to meet this claim element.

The instant claims further recite, in addition to the tiotropium compound and the ciclesonide compound, "a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose." Neither of Nishimura or Banholzer provide any teaching regarding a composition containing such a particular excipient. Further, the Office action provides no reasoning as to why a composition including this element would be obvious to one of ordinary skill in the art. For this additional reason, therefore, the combined references fail to meet the claim recitations.

For both of the above reasons, it is urged that the cited prior art fails to meet at least two elements of the claims and no reason is provided as to why these elements would be obvious. Thus, the cited references do not establish a prima facie case for obviousness and the rejection should be withdrawn, at least for this reason.

Although not necessary in the absence of a prima facie case for obviousness, applicants submit that there is data to show unexpected advantages for applicants' particular combination. Provided with this reply is data showing the unexpected advantages of the claimed combination. The data are not currently in declaration form since, for the reasons stated above, the data may not be necessary. If considered necessary, applicants will re-submit the data in declaration form. The data show that the combination of tiotropium and ciclesonide provide a surprising and synergistic advantageous benefit in bronchoprotective activity. Treatment with the combination of these specific actives gave a bronchoprotective

effect significantly more than the sum of the activities achieved with each separately. Ciclesonide applied at 0.1 mg/kg only induced slight bronchoprotection of about 5% ± 10 %, 3 hours after drug inhalation which remained constant over 24 hours. Tiotropium bromide displayed a dose-dependent bronchoprotection which reached 35% ± 25 % at 0.06 µg/kg, 3 hours after inhalation. The compound retained at the end of the study a bronchoprotection of 12% ± 7 %. The combination of ciclesonide (0.1 mg/kg) and tiotropium bromide (0.06 µg/kg) resulted in an unexpected super-additive bronchoprotection of 49% ± 7 % at 3 hours and of 41% ± 14 % after 24 hours. The combined administration of tiotropium bromide and ciclesonide resulted in a clearly synergistic bronchoprotection in this model. In particular the effect of the combination was significantly higher than the sum of the values of the respective mono-therapies. Such synergistic effect could not have been expected from the cited prior art. Certainly, the references fail to provide any suggestion of the advantage of applicants' particular combination since neither of the references provide any suggestion to use ciclesonide, particularly, together with a tiotropium compound. Further, even for the combination of a different anticholinergic and steroid in Nishimura, there is no suggestion of synergistic effect. The data of unexpected, synergistic advantages, thus, provides further support for the nonobviousness of the claimed invention. If the references established a prima facie case of obviousness, this proof of nonobviousness would overcome the prima facie case. Thus, it provides an independent basis for withdrawal of the rejection.

For all of the above reasons, it is urged that the cited prior art, considered as a whole on the record, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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